

### Three students of the IRB successfully defended their PhD thesis

**Dr. Mara Messi** graduated in Molecular Biology at the University of Zurich. In April 2000 she entered the PhD program of the IRB in the group of Dr. Federica Sallusto and in July 2003 she defended her thesis on the 'Regulation of cytokine gene expression in human effector and memory T lymphocytes' at the University of Bern.



Mara Messi investigated the stability and flexibility of cytokine gene expression in human T helper (Th) cells. She discovered that effector memory Th1 and Th2 cells *in vivo* contain acetylated histones associated with the IFN- $\gamma$  and IL-4 promoters, respectively. This epigenetic modification contributes to confer and possibly maintain the memory for cytokine production through cell divisions. Furthermore, she found that human T cells display a high degree of flexibility that is not shared by mouse T cells. This study is published in *Nat. Immunol.* (2003) 4:78-86.

She also investigated the regulation of cytokine gene expression in activated human T cells involved in ongoing chronic inflammatory responses *in vivo* (rheumatoid arthritis, atopic dermatitis). This study confirmed previous findings and provided new information on the molecular and cellular aspects of T cell-mediated immunopathologies.

**Dr. Elisabetta Traggiai** graduated in Biology at the University of Pisa. She started in April 2000 her doctorate at the Department of Neurological Science of the University of Florence. In June 2003 she defended her thesis on the 'Characterization and regulation of T and B autoreactivity to myelin basic protein (MBP) in Multiple Sclerosis'.

In November 2001 Elisabetta Traggiai joined the group of Prof. Antonio Lanzavecchia at the IRB where she investigated the mechanisms involved in secondary antibody responses and in the maintenance of long-term serological memory. She tested the hypothesis that memory, but not naïve B cells, are continuously activated to proliferate and differentiate into plasma cells *in vitro* and *in vivo* in response to polyclonal stimuli, such as bystander T cell help or Toll Like Receptor (TLR) agonists, thus maintaining a constant antibody production in the absence of antigen. The results of this study were published in *Science* (2003) 298: 2199-2202.



She performed a quantitative analysis of the secondary immune response to a thymus dependent antigen to reveal the relative contribution of antigen induced short- and long- lived plasma cells versus polyclonal activation of all memory B cells. Antigenic boost sustains high levels of serum antibodies only for a few months, while polyclonal activation sustains low levels of protective antibodies for a human life time. Published in *Vaccine* (2003) S235-S237.

**Dr. Nadia Bernasconi** graduated in Biochemistry and Molecular Biology at the University of Southern California at Los Angeles. In August 2000 she entered the PhD program of the IRB in the group of Prof. Antonio Lanzavecchia and in July 2003 she defended her thesis on the 'Selective response of human memory B cells to polyclonal activators: a mechanism maintaining serological memory' at the University of Fribourg, Switzerland.



Nadia Bernasconi studied the requirements for proliferation and differentiation of human naïve, IgM<sup>+</sup> memory and switch memory B cells. She found that, in contrast to naïve B cells, which are dependent on BCR signaling, memory B cells can be selectively activated by polyclonal stimuli such as CpG, cytokines or T cell help, in the absence of antigen. Based on these findings she considered the possibility that a continuous polyclonal activation of memory B lymphocytes may sustain plasma cell generation and antibody production resulting in long term serological memory. The results were published in *Science* (2002) 298:2199-2202.



In another chapter of her thesis she investigated the role of Toll like receptors (TLRs) in human B cell activation. She found that in human naïve B cells, most TLRs are expressed at low to undetectable levels, but the expression of TLR9 and TLR10 is rapidly induced following B-cell-receptor (BCR) triggering. In contrast, memory B cells express several TLRs at constitutively high levels. The requirement of BCR to induce expression of TLRs in human naïve B cells prevents polyclonal activation in a primary response and restricts the stimulation to antigen-specific B cells. The constitutive expression of TLRs in memory B cells allows a polyclonal activation of the entire memory pool. Thus, in human B cells TLRs are downstream of BCR and play a role both in the primary response and in the memory phase. Published in *Blood* 2003;101:4500-4504.

***Two PhD students of the IRB receive the ASIRB-ROCHE research award 2002***

On March 14<sup>th</sup>, 2003 Nadia Bernasconi and Elisabetta Traggiai received the 2002 research award from ASIRB (Associazione della Svizzera italiana per la Ricerca Biomedica) and Roche-Diagnostics for their work on 'Polyclonal activation of human memory B cells and maintenance of serological memory'. The award distinguishes excellence in biomedical research of young scientist in Switzerland to promote scientific activities in Ticino. The studies performed by Nadia Bernasconi and Elisabetta Traggiai were part of their PhD-theses developed at the IRB.